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Ondansetron does not reduce the shivering threshold in healthy volunteers

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Background. Ondansetron, a serotonin-3 receptor antagonist, reduces postoperative shivering. Drugs that reduce shivering usually impair central thermoregulatory control, and may thus be useful for preventing shivering during induction of therapeutic hypothermia. We determined, therefore, whether ondansetron reduces the major autonomic thermoregulatory response thresholds (triggering core temperatures) in humans.

Methods. Control (placebo) and ondansetron infusions at the target plasma concentration of 250 ng ml^{-1} were studied in healthy volunteers on two different days. Each day, skin and core temperatures were increased to provoke sweating; then reduced to elicit peripheral vasoconstriction and shivering. We determined the core-temperature sweating, vasoconstriction and shivering thresholds after compensating for changes in mean-skin temperature. Data were analysed using *t*-tests and presented as means (SDs); $P<0.05$ was taken as significant.

Results. Ondensetron plasma concentrations were 278 (57), 234 (55) and 243 (58) ng ml^{-1} at the sweating, vasoconstriction and shivering thresholds, respectively; these corresponded to ≈50 mg of ondansetron which is approximately 10 times the dose used for postoperative nausea and vomiting. Ondansetron did not change the sweating (control 37.4 (0.4)°C, ondansetron 37.6 (0.3)°C, $P=0.16$), vasoconstriction (37.0 (0.5)°C *vs* 37.1 (0.3)°C; $P=0.70$), or shivering threshold (36.3 (0.5)°C *vs* 36.3 (0.6)°C; $P=0.76$). No sedation was observed on either study day.

Conclusions. Ondansetron appears to have little potential for facilitating induction of therapeutic hypothermia.

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Overwhelming evidence from animal studies indicates that even mild hypothermia provides substantial protection against cerebral[1] and myocardial ischaemia.[2] In humans, mild hypothermia improves outcome after cardiac arrest.[3]

Many studies of therapeutic hypothermia target core temperatures between 33 and 34°C. The ability to induce even mild therapeutic hypothermia in patients having acute myocardial infarction or stroke may be compromised because small reductions in core temperature trigger aggressive thermoregulatory defences,[4] such as shivering, which may be harmful. Various drugs have been shown to impair thermoregulatory defences,[5 6] but even the best have limited efficacy and substantial side-effects. Drugs that moderate thermoregulatory defences against cold without causing serious side-effects would thus be of considerable clinical interest.

Serotonin [5-hydroxytryptamine (5-HT)] is a critical thermoregulatory neurotransmitter.[7–9] In humans, tramadol, a 5-HT reuptake inhibitor, prevents postanaesthetic shivering,[10] and in non-anaesthetized individuals, it decreases the core temperature that triggers shivering (the shivering threshold) by approximately 0.9°C.[11]

The role of the 5-HT_{1A} receptor subtype in 5-HT-mediated hypothermia is well established largely

based on data using 8-hydroxy-[*N*-*n*-dipropyl-*N*-(3′-iodo-2′-propenyl) amino] tetralin (8-OH-DPAT) as a ligand.[12] Although the evidence of involvement of 5-HT_3 receptor subtype in 5-HT-mediated thermoregulation is scarce, a serotonin 5-HT_3 agonist can induce hyperthermia in rats,[7] which is attenuated by pretreatment with a 5-HT_3 antagonist. Furthermore, when given alone, 5-HT_3 antagonists induce hypothermia.[9] As one can expect from these effects in rats, 5-HT_3 antagonists prevent postanaesthetic shivering in humans.[13] They may thus inhibit shivering, perhaps enough to facilitate induction of therapeutic hypothermia. Thus we tested the hypothesis that ondansetron, a prototypical 5-HT_3 antagonist, reduces the sweating, vasoconstriction, and shivering thresholds—and that the reduction is clinically important (i.e. $\geqslant 1^{\circ}C$).

Methods

With approval of the Human Studies Committee at the University of Louisville and written informed consent, we studied 10 healthy volunteers. None was obese, taking medication, or had a history of thyroid disease, dysautonomia or Raynaud's syndrome.

Each volunteer was studied on two randomly assigned days: (1) control (placebo) and (2) ondansetron hydrochloride (GlaxoSmithKline, Research Triangle Park, NC, USA) at a target plasma concentration of 250 ng ml^{-1}. Volunteers were blinded as to which solution they received on each study day. The volunteers fasted for 8 h before the start of each study day. They dressed minimally and rested supine on a standard operating room table. Ambient temperature was maintained near 21°C and humidity at 25%.

A 14 gauge catheter was inserted in a right antecubital vein for blood sampling and an 18 gauge catheter was inserted in a left forearm vein for ondansetron or placebo administration. Blood for ondansetron analysis was sampled from the catheter inserted in right antecubital vein before drug administration (blank sample) and at each threshold. Blood was centrifuged, and the plasma was removed and stored at −40°C until analysis.

Ondansetron was infused using a target-controlled infusion with a Stanpump program based on pharmacokinetic data from Colthup and colleagues[14] and de Alwis and colleagues[15] at a target plasma concentration of 250 ng ml^{-1}. This corresponds to ≈50 mg of ondansetron over the approximately 2.5 h study period. A similar volume of normal saline was infused on the control day. The infusion began at the start of thermal manipulation and continued until shivering was detected.

Skin and core temperatures were gradually increased with an Allon circulating-water garment (MTRE, North Industrial Park, Israel) and a whole-body convective-air warming coverlet and air heater-blower unit (Bair Hugger Model 250, Augustine Medical, Inc., Eden Prairie, MN, USA) until sweating occurred. Subsequently, skin and core temperature were decreased with an Allon circulation-water garment and convective-air cooling coverlet (PolarAir, Augustine Medical Inc., Eden Prairie, MN, USA) until shivering occurred. The volunteer's body was insulated with the warming and cooling devices mentioned; except for the head, and right forearm and hand, which were used for fingertip blood flow measurement.

Core temperature was measured at the tympanic membrane using Mon-a-therm thermocouples (Tyco-Mallinckrodt Anesthesiology Products, Inc., St Louis, MO, USA). The aural probes were inserted by the volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The aural canal was occluded with cotton and taped in place.

Mean skin-surface temperature and cutaneous heat transfer were calculated from measurements at 15 area-weighted sites. Temperatures were recorded at 1 min intervals from thermocouples connected to calibrated Iso-Thermex® thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments, Corp., Columbus, OH, USA).

Sweating was continuously quantified on the left upper chest using a ventilated capsule.[4] We considered a sweating rate >40 g m^{-2} h^{-1} for at least 5 min to be significant.[16] Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5 min intervals.[17] The vasoconstriction threshold was determined *post hoc* by an observer blinded to treatment and core temperature.

As in previous similar studies,[16] we used systemic oxygen consumption to quantify shivering. A Deltatrac metabolic monitor (SensorMedics Corp., Yorba Linda, CA, USA) was used in canopy mode. Initiation of the shivering threshold was determined *post hoc* by an observer blinded to treatment and core temperature. The same observer determined the shivering threshold for all subjects. End-tidal carbon dioxide was sampled from a catheter inserted into one nostril; gas removed from the catheter was returned to the canopy of the metabolic monitor.

Heart rate, end-tidal carbon dioxide and oxyhaemoglobin saturation (Sp_{O_2}) were measured continuously, and blood pressure was determined oscillometrically at 5 min intervals at the left ankle.

An investigator blinded to core temperature and treatment evaluated sedation using the responsiveness component of the observer's assessment of alertness/sedation (OAA/S) score (Table 1)[18] at 15 min before starting drug administration, before thermal manipulation started and at each threshold.

Before extraction, plasma samples for ondansetron analysis were allowed to thaw at room temperature and vortexed. To 1 ml of plasma, 1 ml 0.1 M sodium phosphate buffer, pH 6.0 and internal standard (prazosine hydrochloride, Sigma–Aldrich, USA) was added and vortexed. Clean

Table 1. Responsive component of the OAA/S scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is spoken loudly, repeatedly, or both
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking

Screen solid phase extraction columns (CSDAU-203, World Wide Monitoring, United Chemical Technologies, Inc., Bristol, PA, USA) were preconditioned with 3 ml of methanol, 3 ml of deionized water and 3 ml of 0.1 M sodium phosphate buffer before the plasma samples were loaded (about 0.5 ml min^{-1}). The cartridges were rinsed with 3 ml of deionized water, 2 ml of 1 M acetic acid, 3 ml of methanol and then dried under vacuum for at least 5 min. The extracts were then eluted from the cartridge with 3 ml of freshly prepared dichloromethane–isopropanol–ammonium hydroxide 25% (39:10:1; vol: vol:vol, prepared with sonication) by gravity filtration.

The eluate was evaporated to dryness under nitrogen stream in a water bath at about 40°C. The residues were redissolved in 200 μl mobile phase mixture, briefly mixed in an ultrasonic bath, and loaded into auto-sampler vials. Samples were analyzed by HPLC (Merck-Hitachi, L6200A and AS-2000A, Hitachi, Ltd, Tokyo, Japan) with UV detection (Merck-Hitachi, DAD L-4500) at 250 nm. Aliquots of 20 μl were injected onto a Nucleodur 100-5 CN-RP (Macherey-Nagel, CH), 250 mm, 4 mm ID column with an 8 mm precolumn. The mobile phase consisted of 40% acetonitrile, 60% 20 mM bisodiumphosphate buffer, pH 5.4. The flow rate was 1.5 ml min^{-1} and operating temperatures were 35°C. The data were processed with proprietary HPLC control software (Merck-Hitachi, Model D-7000, Hitachi Instruments, Inc., San Jose, CA, USA).

Retention times of the internal standard and ondansetron (Zofran, GlaxoSmithKline plc, Middlesex, UK) were 2.96 and 3.36 min, respectively. Calibration curves with spiked and extracted plasma passed through the origin and were linear in the calibration range 150–400 ng ml^{-1} with correlation coefficient values of $r^2 \geqslant 0.99$. The intraday and interday coefficients of variation were 2.5 and 3% for quality control samples containing 250 ng ml^{-1} ondansetron, respectively. For ondansetron, the limit of quantification (S/N=10) was 15 ng ml^{-1} and the recovery was ⩾95%.

Statistical analysis

The cutaneous contribution to the thermoregulatory responses—sweating,[19] vasoconstriction and shivering—is linear.[20] We thus used measured skin and core temperatures in °C at each threshold to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature. For this purpose, we used equation (1) that corrects core temperature for cutaneous temperature, providing response thresholds that would have been observed at a designated core temperature.

$$T_{\text{core(calculated)}} = T_{\text{core}} + \left(\frac{\beta}{1-\beta}\right)[T_{\text{skin}} - T_{\text{skin(designated)}}] \quad (1)$$

We have previously described the derivation and validation of this equation.[16] We used a β of 0.1 for sweating[19] and a β of 0.2 for vasoconstriction and shivering.[20] The designated skin temperature was set at 34°C, a typical intraoperative value.

We determined that a sample size of 10 would detect a 0.5°C difference in shivering thresholds between control and drug days with 90% power. Based on a similar study conducted with the same design in our laboratory with doxapram,[21] we assumed that the difference in shivering thresholds on the two study days would have a SD of 0.44 and correlation of 0.75.

Oxygen consumption and calculated respiratory quotient were averaged during baseline (before commencement of drug infusion), during the cooling phase before shivering and during shivering, respectively. The averaged values were then compared with two-way ANOVA (two factors; drug, period) and *post hoc* Bonferroni/Dunn tests.

Ambient temperature, humidity, mean arterial pressure, heart rate, Sp_{O_2} and end-tidal carbon dioxide on each study day were averaged within each volunteer across the warming and cooling periods; the resulting values were then averaged among volunteers. Results for each study day were compared using Wilcoxon signed-rank tests or paired *t*-tests. Plasma concentrations of ondansetron at each threshold were compared using one-way ANOVA. All results are presented as means (SD) or median (range), as appropriate; $P<0.05$ was considered statistically significant.

Results

Seven of the participants were males and three were females. They were 24 (19–31) yr old, weighed 73 (14) kg, and were 174 (7) cm tall. Among the factors that might have influenced the thermoregulatory thresholds, ambient temperature was significantly higher on ondansetron days than on the control days, but the average difference was only 0.7°C (P=0.004; Table 2).

Plasma ondansetron concentrations were similar at each threshold, ≈250 ng ml^{-1}. The median dose of ondansetron was 49 mg and ranged from 36 to 70 mg. None of the study participants was sedated at any time on either study day, and OAA/S scores remained 5 for all volunteers throughout the study.

The sweating thresholds were similar on the control [37.4 (0.4)°C] and ondansetron [37.6 (0.3)°C] days (P=0.16) [mean (SD)]. Ondansetron did not alter either the vasoconstriction threshold [control 37.0 (0.5)°C;

Table 2. Potential confounding factors. Values were recorded at 5 min intervals and averaged over the sweating-to-shivering period. Results are presented as medians (range); results were compared with Wilcoxon signed-rank test

	Control day	Ondansetron day	*P*-value
Mean arterial blood pressure (mm Hg)	88 (84–106)	92 (72–102)	0.867
Heart rate (beats min^{-1})	71 (57–95)	72 (55–88)	0.754
End-tidal carbon dioxide (kPa)	5.3 (5.2–5.7)	5.5 (4.4–6.1)	0.863
Oxygen saturation (%)	98 (97–99)	97 (96–98)	0.375
Ambient temperature (°C)	24.6 (24.0–26.3)	25.7 (24.8–26.7)	0.004
Relative humidity (%)	28.2 (5.4–40.6)	13.1 (4.5–38.5)	0.160

Table 3. Plasma ondansetron concentrations, mean-skin temperatures, core temperatures and calculated thermoregulatory thresholds. Thresholds were calculated based on a designated mean-skin temperature of 34°C. Results are presented as means (SD) (range). Only the threshold values were statistically compared, and none differed significantly

	Control	Ondansetron
Sweating		
Mean skin (°C)	36.7 (0.5)	36.9 (0.3)
Core (°C)	37.1 (0.4)	37.2 (0.3)
Threshold (°C)	37.4 (0.4)	37.6 (0.3)
Ondansetron concentration (ng ml^{-1})	–	278 (57) (226–380)
Vasoconstriction		
Mean skin (°C)	33.5 (1.2)	33.6 (0.7)
Core (°C)	37.1 (0.3)	37.2 (0.3)
Threshold (°C)	37.0 (0.5)	37.1 (0.3)
Ondansetron concentration (ng ml^{-1})	–	234 (55) (161–325)
Shivering		
Mean skin (°C)	30.7 (1.3)	30.4 (1.8)
Core (°C)	37.1 (0.3)	37.1 (0.3)
Threshold (°C)	36.3 (0.5)	36.3 (0.6)
Ondansetron concentration (ng ml^{-1})	–	243 (58) (178–338)

ondansetron 37.1 (0.3)°C; *P*=0.70] or the shivering threshold [control 36.3 (0.5)°C; ondansetron 36.3 (0.6)°C; *P*=0.76] (Table 3 and Fig. 1).

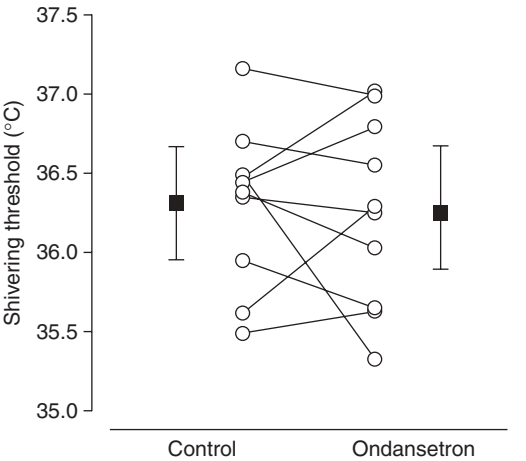

Fig 1 Shivering thresholds in 10 healthy volunteers. The open circles show the shivering threshold for each volunteer on the control and ondansetron study days; the filled squares are the group means (SD). The shivering threshold was similar on the control day and ondansetron day, *P*=0.76.

Discussion

Plasma ondansetron concentrations were similar at each of the three thermoregulatory thresholds and were near our target concentration of 250 ng ml^{-1}. The Stanpump program, based on pharmacokinetic data of Colthup and colleagues[14] and de Alwis and colleagues[15] thus proved reliable. According to the 2003 edition of the *Physician's Desk Reference*, a single 32 mg bolus of ondansetron—the dose used for prevention of chemotherapy-induced nausea and vomiting—yields a maximum plasma concentration of 264 ng ml^{-1}. We thus chose a target ondansetron plasma concentration of 250 ng ml^{-1}. Our modelling suggested that the total dose after a 5 h infusion would be 60 mg in a 70 kg volunteer, which is less than that used for prophylaxis of chemotherapy-induced nausea and emesis in clinical trials.[22] In fact, the total dose we used averaged 49 (12) mg.

We targeted a plasma ondansetron concentration that might be used for treatment of chemotherapy-induced nausea and vomiting; therefore, our volunteers received roughly 10 times the dose normally used for prevention of postoperative nausea and vomiting.[23] But even at this high concentration, there was no perceptible effect of ondansetron on the sweating, vasoconstriction or shivering thresholds. It is thus apparent that ondansetron alone cannot be used to facilitate induction of therapeutic hypothermia, and there is little reason to believe that it will prove to be a useful adjunct to other anti-shivering medications.

Meta-analysis indicates that meperidine 25 mg, clonidine 150 μg, ketanserin 10 mg and doxapram 100 mg are effective anti-shivering agents.[24] Nalbuphine also prevents postoperative shivering[25] and has been formally evaluated for shivering threshold suppression.[26] Several drugs that are unquestionably effective for postoperative shivering actually reduce the shivering threshold only slightly. For example, clonidine and doxapram reduce the shivering threshold only about 0.5°C, but are nonetheless effective anti-shivering agents. The reason, presumably, is that many postoperative patients have core temperatures only slightly below the normal shivering threshold, which is about 35.5°C.[27] Other effective anti-shivering drugs reduce the shivering threshold even more, typically about 1°C (Table 4). Ondansetron thus appears to be unique in reportedly reducing the incidence of postoperative shivering,[13] but not in reducing the shivering threshold, even at doses 10 times those used for treatment of postoperative nausea and vomiting.

Postoperative rhythmic shivering-like muscular activity is a complex phenomenon. Most of such activity is thermoregulatory, and most of it is normal shivering. However, some are expressed as tonic stiffening that occurs when residual concentrations of volatile anaesthesia are 0.2–0.4

Table 4. Drugs used for postoperative shivering and their effects on the shivering threshold. The 'Dose or concentration' column refers to threshold reduction. Various doses were used for treatment of shivering, but usually as a bolus without controlling pharmacokinetics or measurement of plasma drug concentration; only selected examples of shivering treatment are included

	Treatment of shivering	Reduction in shivering threshold (°C)	Dose or concentration (ng ml^{-1})
Clonidine	Piper and colleagues,[33] Horn and colleagues[29]	0.6 (0.3)[34]	75 μg
Nefopam	Bilotta and colleagues[35]	0.9 (0.4)[6]	55
Tramadol	De Witte and colleagues[36]	0.9[11]	205
Meperidine	Piper and colleagues,[33] Wang and colleagues[25]	1.2[37]	0.3
Doxapram	Singh and colleagues[38]	0.5[21]	2.6
Nalbuphine	Wang and colleagues[25]	1.1[26]	30

of the minimum alveolar concentration. Other tremors are manifested as clonic tremors similar to pathological clonus or physiological action tremor, which appear to be triggered by low concentrations (i.e. 0.1 minimum alveolar concentration) of volatile anaesthetics.[28] Other shivering-like tremors are not thermoregulatory at all[29] and appear to be facilitated by pain.[30] It is thus possible that 5-HT_3 antagonists inhibit non-thermoregulatory shivering-like activity.

A limitation of our study was that the mean ambient temperature was significantly greater on the ondansetron day than the control day. However, the temperatures differed by only 0.6°C. More importantly, skin temperature, except for the head and the right forearm, was deliberately manipulated throughout the study period. Skin temperature contributes 10% to autonomic control of sweating[19] and 20% to control of vasoconstriction and shivering,[20] and thermal sensitivity of the face is greater than that of the remaining skin surface.[31] However, the lower arm and face make up a small portion of the total skin surface. We have previously demonstrated that neither arm nor face warming influences the shivering threshold in non-anaesthetized human volunteers.[32] The small difference in ambient temperature on the two study days is thus unlikely to compromise the thermoregulatory threshold outcomes.

In summary, ondansetron at a plasma concentration of ≈250 ng ml^{-1}, that is at a dose near that used to treat chemotherapy-induced nausea and emesis, did not significantly alter the core-temperature thresholds triggering sweating, vasoconstriction or shivering. The drug, therefore, appears to have little potential for facilitating induction of therapeutic hypothermia.

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